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UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF CALIFORNIA

IN RE: INCRETIN-BASED THERAPIES PRODUCTS LIABILITY LITIGATION

Relates to: ALL CASES

Master File No.: 3:13-md-02452-AJB-MDD

MDL – 2452

PLAINTIFFS' MEMORANDUM IN OPPOSITION TO DEFENDANTS' MOTION FOR SUMMARY JUDGMENT ON THE AFFIRMATIVE DEFENSE OF PREEMPTION

[REDACTED-PUBLIC VERSION]

Date: To be determined
Time: To be determined
Courtroom: 3B
Judge: Hon. Anthony J. Battaglia
Magistrate: Hon. Mitchell D. Dembin

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I. INTRODUCTION

The preemption analysis in this case is straightforward. The Court begins with a presumption against preemption: "the CBE regulation permits changes, so a drug manufacturer will not ordinarily be able to show that there is an actual conflict between state and federal law such that it was impossible to comply with both." *Albrecht* at 1679.[1] Thereafter, the Court asks two questions:

- Have the Defendants shown that the FDA "informed the drug manufacturer that the FDA would not approve a change to the drug's label to include that warning" through an "agency action carrying the force of law?" *Albrecht* at 1672, 1679.
- Have the Defendants shown they "fully informed the FDA of the justifications for the warning," providing both an "evaluation or analysis concerning the specific dangers that would have merited the warning" and "all material information?" *Albrecht* at 1672, 1678, 1680.

When a drug manufacturer cannot answer "yes" to both questions, it has no preemption defense.[2] Further, a drug manufacturer must directly address these questions, rather than raising only hypotheticals or possibilities.[3] In this case, Defendants cannot answer "yes" to either question, much less both:

- Defendants do not and cannot allege the FDA informed them that it would not approve a change to the drugs' label to warn about pancreatic cancer;
- Defendants do not and cannot allege the FDA rejected a proposed label change for pancreatic cancer with an agency action carrying the force of law;

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[1] *Merck Sharp & Dohme Corp. v. Albrecht*, 139 S. Ct. 1668 (2019).

[2] *Albrecht* at 1678 ("In a case like *Wyeth*, showing that federal law prohibited the drug manufacturer from adding a warning that would satisfy state law ***requires the drug manufacturer to show*** that it fully informed the FDA of the justifications for the warning required by state law and that the FDA, in turn, informed the drug manufacturer that the FDA would not approve changing the drug's label to include that warning." Emphasis added.)

[3] *Albrecht* at 1678-1679 ("[A]s we have cautioned many times before, the possibility of impossibility is not enough. … The existence of a hypothetical or potential conflict is insufficient to warrant the pre-emption of the state statute." Quotations omitted.).

- The Ninth Circuit already held that Defendants withheld material information from the FDA;[4]
- Defendants do not and cannot allege they informed the FDA of the justifications for a pancreatic cancer warning *at all*, much less "fully informed the FDA of the justifications;" and,
- Discovery has uncovered still more material information that was either not provided to FDA or was not incorporated into an analysis concerning the specific dangers that would have justified the pancreatic cancer warning.

Each of these issues *independently* eliminates any preemption defense. Cumulatively, they demonstrate this renewed preemption motion is frivolous.

II. FACTS

1. Plaintiffs allege Defendants' medications cause or contribute to the progression of pancreatic neoplasia and lesions into pancreatic cancer, including malignancies. It is undisputed that Defendants' medications do not warn about these conditions in any way, and that Defendants have never submitted to the FDA any proposed labeling that would include pancreatic cancer, pancreatic malignancy, or pancreatic neoplasm among their medications' warnings or adverse reactions.

2. Defendants have generally taken the position that DPP-4 inhibitors and GLP-1 receptor agonists should not be viewed as a single drug class with regard to pancreatic adverse events. [redacted]

[redacted]

[4] *In re Incretin-Based Therapies Prod. Liab. Litig.*, 721 Fed.Appx. 580 (9th Cir. 2017).
[5] Exhibits are attached to the Declaration of Tor Hoerman filed herewith.

3. Admitted that there is no circumstance in which Defendants' medications specifically or incretin mimetics in general are the only option for patients.

4. Denied. No leading medical organizations recommend incretin mimetics as a treatment for type 2 diabetes. Rather, metformin, initially approved at FDA by Plaintiffs' expert Dr. Fleming, is recommended, and thereafter other medications are potentially added as a second-line treatment, sometimes including DPP-4is and GLP-1 RAs. There is no circumstance in which DPP-4is or GLP-1 RAs are the only recommended option, but there are circumstances in which they are *not* the recommended option, such as if the patient has a risk of heart failure or chronic kidney disease, or if cost is a major issue. See ADA standard, Figure 9.1, attached as Ex. D to Boehm Decl.

5. Denied. Defendants' arguments regarding 21 U.S.C. § 355(d) were presented to the Supreme Court by Defendants themselves and rejected, 6-3. See § IV(A)(1), *infra*.

6. Denied. The manufacturer retains full responsibility for the labeling and has the power to alter it, and approval of a label does not in any way support impossibility preemption. "[T]he CBE regulation permits changes, so a drug manufacturer will not ordinarily be able to show that there is an actual conflict between state and federal law such that it was impossible to comply with both." *Albrecht* at 1679. See also *In re Testosterone Replacement Therapy*, 430 F.Supp.3d 516, 529-30 (N.D. Ill. Dec. 30, 2019) ("Actavis's argument is unpersuasive because it assumes that the FDA's approval of the Androderm label in April 2012 constitutes 'clear evidence' that it would have rejected an attempt by Actavis to add the relevant warnings between 1995 and October 2012 based on the information available during that time.").

7. Denied. Defendants themselves presented this *exact same* argument to the Supreme Court, which rejected it, 6-3, just as it had rejected it in *Levine*. See *Albrecht* at 1677 (discussing the 2007 Amendments to the FDCA); see also § IV(A)(1), *infra*.

8. Denied. "[I]mportant safety information, like a new contraindication or warning, [ ] should be immediately conveyed to the user." 50 Fed. Reg. 7452. "Causation

need not have been 'definitely established' for a warning to be required to appear in labeling, but rather there need only be 'reasonable' evidence of a causal association with the drug, a standard that could be met by a wide range of evidence." 73 Fed. Reg. 49603. The FDA Guidance on Warnings and Precautions, Dkt 1166-11, notes at p. 3 that "Some factors to consider in assessing whether there is reasonable evidence of a causal association include: … whether the adverse event rate in the drug treatment group exceeds the rate in the placebo and active-control group in controlled trials," which is true for all the drugs in this litigation, as discussed below. Another example of the "wide range of evidence" used by the FDA is "biological plausibility plus an imbalance in reporting of a particular event," which is also true for all the drugs in this litigation. See Ex. 3, Fleming Dep., 148:15-22.

9. Denied. Defendants have misrepresented the labeling regulation, as described above. Moreover, Defendants' description of "federal law" is contrary to *Albrecht*, which specifically held that impossibility preemption could not be created by imaginary "federal law" generated by a drug company's claims about hypothetical situations. Rather, it needs to be grounded in a real agency action "carrying the force of law," such as "formally rejecting a warning label that would have been adequate under state law" via a complete response letter issued pursuant to 21 C.F.R. § 314.110(a). Defendants have nothing of the sort here.

10. Denied. Defendants' quotation arises from a discussion in *Albrecht* of "the hierarchy of label information," with boxed warnings above countraindications, above warnings, above adverse reactions. *Albrecht* at 1673. Plaintiffs' claims concern the latter two sections. Moreover, the citation in *Albrecht* which Defendants omitted is to the same regulatory action described above, in which the FDA stated "Causation need not have been 'definitely established' for a warning to be required to appear in labeling, but rather there need only be 'reasonable' evidence of a causal association with the drug, a standard that could be met by a wide range of evidence." 73 Fed. Reg. 49603.

11. Denied. Defendants' argument, based on a 1979 FDA action, that preemption can be established by the possibility of a misbranding prosecution as a result of overwarning was rejected by *Levine* and rejected again by *Albrecht*. *Wyeth v. Levine*, 555 U.S. 555, 570 (2009) ("the very idea that the FDA would bring an enforcement action against a manufacturer for strengthening a warning pursuant to the CBE regulation is difficult to accept"); *Albrecht* at 1679 ("The existence of a hypothetical or potential conflict is insufficient to warrant the pre-emption of the state statute." Quotation omitted.)

12. Admitted that the FDA has never taken any action, carrying the force of law, with regard to the inclusion of pancreatic cancer on Defendants' labeling. This fact alone precludes preemption as a matter of law. Defendants' other characterizations are denied.

13. Denied.

a. Legally, FDA "monitoring" is not relevant to preemption, even after the 2007 Amendments. *Albrecht* at 1677 ("in the 2007 Amendments to the FDCA, Congress simultaneously reaffirmed the manufacturer's obligations and referred specifically to the CBE regulation, which both reflects the manufacturer's ultimate responsibility for its label and provides a mechanism for adding safety information to the label prior to FDA approval." Quotations to *Levine* omitted.) In *Albrecht*, "the FDA [had] long been aware that Fosamax could theoretically increase the risk of atypical femoral fractures," and yet that did not create impossibility preemption because actions taken by the FDA do not fulfill Defendants' obligation to show they "fully informed the FDA of the justifications for the warning required by state law." *Albrecht* at 1675, 1678.

b. Factually, Defendants have never fully informed the FDA of the justifications for a pancreatic cancer warning. As of September 2009, Defendants were also concealing, misrepresenting, or failing to present to FDA [redacted]

[redacted] See § IV(C)(4)(iii), *infra*.

14. Denied. Contrary to Defendants' description, the FDA's 2013 Public Safety Communication did not state FDA was "conduct[ing] a comprehensive evaluation" nor that FDA "would consider the totality of the available scientific data." DEF MEM, p. 7. Notably, FDA said "FDA will communicate its final conclusions and recommendations when its review is complete," but that has *not* yet happened. The Public Safety Communication is still on the FDA's website without any amendments or updates, and without even a link to the 2014 NEJM article. In fact, the current page says it was last reviewed "02/21/2018," long after the other evidence identified by Defendants. Thus, the FDA's *current* position is that the FDA has not completed its review.

15. Denied. The NEJM article is, by regulation, an "informal communication" that "does not necessarily represent the formal position of FDA," and cannot constitute an agency action carrying the force of law, as is necessary to support preemption. Per 21 CFR 10.85(k), "[a] statement or advice given by an FDA employee orally, or given in writing but not under this section [relating to official advisory opinions] or 10.90 [relating to regulations and guidance documents], is an informal communication that represents the best judgment of that employee at that time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed." The NEJM article is the opposite of an "agency action" creating "federal law" as required by *Albrecht*. The FDA's own regulations, 21 CFR 10.85(k), make the NEJM article an "informal communication" that carries no legal weight. Underscoring the *informal* nature of the NEJM article, it has still never been posted on FDA's website, which is the official method by which FDA communicates with healthcare providers and the public.

16. Denied the NEJM article reflects the FDA's position. Per 21 CFR 10.85(k), the NEJM represents only the "best judgment" of the employees who signed it, and does

not represent the FDA's position. Further, as of February 2014, Defendants had yet more safety information they concealed, misrepresented, or failed to present to FDA, including sitagliptin's 6-to-3 pancreatic cancer imbalance in clinical trials (the NEJM article even cites a Merck article that falsely represented the cases as 3-to-3); Health Canada's signal assessment; [redacted]. See § IV(C)(3) & (4), *infra*.

17. Denied the NEJM reflects the FDA's conclusions. Per 21 CFR 10.85(k), the NEJM represents only the "best judgment" of the employees who signed it, and does not represent the FDA's position. The FDA employees listed as co-authors on the NEJM article would not even be responsible for approving or rejecting safety labeling changes to Defendants' medications. That responsibility would fall to the Director, Division of Metabolism and Endocrinology Products ("DMEP"), Office of Drug Evaluation II, who at that time was Mary Parks, who was followed by Jean-Marc Guettier, and then by Mary T. Thanh Hai—none of whom co-authored the NEJM article. Arguably, labeling changes could have been approved or rejected by the Deputy Director for Safety at DMEP, but that was Jennifer Rodriguez Pippins, who also was not a co-author.

18. Denied. FDA exercised congressionally delegated authority to promulgate, via notice-and-comment, a regulation that expressly makes the NEJM article *not* carry the force of law and *not* bind the agency. 21 CFR 10.85(k). Defendants also presented these exact same arguments based on the 2007 Amendments (see DEF MEM, p. 9, citing 21 U.S.C. §§ 355(o)(4), 379d-2(b)) to the Supreme Court in *Albrecht*, which rejected them.

19. Denied. First, the FDA Staff Manual does not take precedence over 21 CFR 10.85(k). Second, the very section of the Manual cited by Defendants says that, for FDA-

Assigned articles, "the views expressed in the article or speech do not necessarily represent the official views or policies of the agency (see 21 CFR 10.85(k))." Third, there is no evidence the NEJM was "FDA-Assigned," and its lead author, Amy Egan, left the FDA shortly thereafter to become a paid expert witness for drug companies.

20. Denied.

21. As Defendants note, the citizen petition was focused primarily on pancreatitis and "ask[ed] the Agency to withdraw Victoza from the market," not to amend the labeling to include pancreatic cancer. The FDA's rejection of the petition did not inform the manufacturers of incretin mimetics that any proposed pancreatic cancer warning would be rejected. Moreover, the citizen petition did not include any of the information Defendants have concealed from the FDA, much less serve as a stand-in for the Defendants "fully informing the FDA of the justifications" for a warning.

22. Denied. The 2014 Saxenda Briefing Document appears to have been scrubbed completely from FDA's website and is no longer available, and thus may have been formally retracted. In any event, the Saxenda Briefing Document begins with a prominent "DISCLAIMER" saying the assessments, conclusions, and recommendations therein "do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office," another indication it is not an agency action carrying the force of law. The document itself does not inform Novo or any other Defendant that the FDA will not approve any labeling change related to pancreatic cancer. Moreover, in addition to all concealed safety data identified above, the Saxenda Briefing Book (p. 16) and FDA's contemporaneous November 10, 2014 "Summary Review for Regulatory Action" on Saxenda states "There have been no reports of exocrine pancreatic cancer from the weight management program to date."[6] Novo knew

[6] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/206321Orig1s000SumR.pdf, p. 23.

that was false. One month earlier, on October 15, 2014, there was a pseudopapillary tumor of the pancreatic body—a type of exocrine pancreatic cancer[7]—in Novo's weight management trial, but Novo did not file its MedWatch report[8] for that case until March 15, 2018, and still fails to report it in its FDA submissions specifically discussing pancreatic cancer, like the PSUR.

23. It is admitted that Defendants cannot identify a single instance of any manufacturer of an incretin-based drug proposing a pancreatic cancer warning, or show "that the drug manufacturer fully informed the FDA of the justifications for the warning required by state law and that the FDA, in turn, informed the drug manufacturer that the FDA would not approve a change to the drug's label to include that warning" by way of an "agency action carrying the force of law." *Albrecht* at 1672, 1679.

24. Denied. The Briefing Book, which bears a disclaimer and is subject to 21 CFR 10.85(k), does not necessarily reflect FDA's position or bind the FDA to anything, much less conclusively describe any "review and evaluation of the pancreatic safety of Victoza and other incretin-based therapies."

25. Denied the Briefing Book reflects FDA's "conclusions." Moreover, as described above, references to "overt pancreatic toxic effects" and clinical data show that the data Defendants misrepresented or failed to disclose to the FDA are highly material to the FDA. In addition to all the prior concealed safety information, for LEADER specifically, Novo lied to the FDA about the expected incidence of pancreatic cancer. Novo commissioned a study that used the records of **208,672** patients who met the inclusion criteria of LEADER and were balanced to match the LEADER population among dozens of demographic, clinical, and comorbidity covariates for the express purpose of identifying

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[7] *See, e.g.,* Shuja, et al, "Solid pseudopapillary tumor: a rare neoplasm of the pancreas," Gastroenterol Rep (Oxf). 2014 May; 2(2): 145–149, stating "Solid pseudopapillary tumor (SPT) of the pancreas is a rare exocrine pancreatic tumor."

[8] NNI-MDL_00000507, Ex. 4.

the expected rate of pancreatic malignancies in the LEADER population. That expected rate was 0.03565 per 100 patient years, strikingly close to the eventual placebo LEADER rate of 0.03, but less than half the liraglutide LEADER rate of 0.08. Novo concealed that study from the FDA and then, in its submission to the Advisory Committee, lied by claiming the expected rate in LEADER was 0.05-0.08. See § IV(C)(4)(ii), *infra*.

26. Admitted that Novo did not propose a pancreatic cancer warning.

27. Denied. See response to #6 and #23. A labeling approval is not evidence supporting preemption.

28. Denied. Defendants presented this argument regarding the FDAAA to the Supreme Court in *Albrecht* and it was rejected, 6-3. See § IV(A)(1), *infra*. Their argument here is substantively identical to the argument the Supreme Court refused to accept:

- **Petitioner Merck's Reply Brief, *Albrecht*, pp. 5, 7:**
  - "Once a manufacturer discharges its duty by bringing a specific risk to the FDA's attention and proposing to warn about it, the agency's denial of that proposal must be understood in light of the duties imposed by the 2007 statutory amendments."
  - "If the agency declines to initiate a § 355(o)(4) process, that means it does not believe the new information justifies a new warning—and that clearly demonstrates the impossibility of adding such a warning."
- ***Amici Curiae* Brief for Pharm. Research and Mfrs. of America, *Albrecht*, p. 4:**
  - "Under the revised statutory regime, when the FDA has considered a potential new safety issue and exercised its scientific judgment to conclude that no new labeling is required, the agency's decision not to adopt such labeling provides dispositive evidence that the FDA would have rejected *any* warning for that particular safety risk, regardless of the language used." "If the agency declines to initiate a § 355(o)(4) process, that means it does not believe the new information justifies a new warning—and that clearly demonstrates the impossibility of adding such a warning."
- **Defendant's Brief in this Case (Dkt 3594-1), p. 35:**
  - "Considering this history and the FDA's labeling mandate under FDAAA, it is clear that the FDA would not approve a pancreatic cancer warning for liraglutide or for any other incretin-based therapy. FDA's continued inaction does represent clear evidence under these facts. The FDA has been focused for many years on the central question at issue in this litigation—whether the labeling for defendants' drugs should include a pancreatic cancer warning."

Defendants' argument was rejected in *Albrecht* and is also inconsistent with its holding, which requires a drug manufacturer to show that it "fully informed the FDA of the justifications for the warning" and that "the FDA, in turn, informed the drug manufacturer that the FDA would not approve a change to the drug's label to include that warning" by way of an "agency action carrying the force of law." *Id.* at 1672, 1679. Defendants improperly seek to reargue and nullify the Supreme Court's decision in *Albrecht*.

III. STANDARD OF REVIEW

As the parties asserting preemption, Defendants carry the burden of proof. *Silkwood v. Kerr-McGee Corp*., 464 U.S. 238, 255 (1984)("it is Kerr-McGee's burden to show that Congress intended to preclude such [state tort] awards"); *Kanne v. Connecticut General Life Ins. Co*., 859 F.2d 96, 99 n. 4 (9th Cir. 1988)("burden is on the defendant to prove the facts necessary to establish" affirmative defense of preemption).

Albrecht reaffirmed these holdings: "**the manufacturer must show**" federal law "prohibited the drug manufacturer from adding any and all warnings to the drug label that would satisfy state law." *Albrecht* at 1678 (emphasis added). Preemption "**requires the drug manufacturer to show** that it fully informed the FDA of the justifications for the warning required by state law and that the FDA, in turn, informed the drug manufacturer that the FDA would not approve changing the drug's label to include that warning." *Albrecht* at 1678 (emphasis added). If the record is ambiguous or arguments are not adequately developed, the manufacturer has failed to meet its burden under *Albrecht*:

> After reviewing the record on appeal, we conclude that Genentech's arguments on this issue were inadequately developed, and that, in any event, the evidence submitted by Genentech in support of its arguments was insufficient to allow us to arrive at any reasonable conclusion regarding the impossibility of Genentech utilizing the CBE process to change the drug concentration statements on its product labeling. Genentech therefore failed to establish its entitlement to summary judgment as to this claim, and the district court erred in concluding otherwise.

In re Genentech Herceptin (Trastuzumab), 960 F.3d 1210, 1240 (10th Cir. 2020)(ordering reversal of summary judgment when manufacturer failed to satisfy preemption burden).

IV. ARGUMENT

The Supreme Court's *Albrecht* decision resolves this motion in favor of Plaintiffs. Since *Albrecht* has been detailed above in §§ I-III, it will not be separately addressed here. Plaintiffs turn instead to debunking Defendants' arguments which, of course, ignore virtually every aspect of *Albrecht*.

A. DEFENDANTS' ARGUMENTS ARE INCOMPATIBLE WITH *ALBRECHT* AND THE NINTH CIRCUIT'S ORDER IN THIS CASE.

Impossibility preemption is not an invitation for innovation. "[W]e acknowledged that meeting the standard we set forth [in *Wyeth*] would be difficult" because "impossibility pre-emption is a demanding defense." *Albrecht* at 1678. Impossibility preemption is such a narrow doctrine that "we have refused to find clear evidence of such impossibility where the laws of one sovereign permit an activity that the laws of the other sovereign restrict or even prohibit." *Id.* Accordingly, "a drug manufacturer will not ordinarily be able to show that there is an actual conflict between state and federal law such that it was impossible to comply with both." *Id.* at 1679.

Defendants cannot point to any FDA action which "informed the drug manufacturer that the FDA would not approve a change to the drug's label to include [the] warning," much less such an agency action "carrying the force of law," *Albrecht* at 1679, so the preemption inquiry ends there. Even if the inquiry could proceed further, it would reach a similarly swift end based upon the Ninth Circuit's ruling in this case:

> Uncertainty about whether the FDA considered the 'new safety information' and whether it would have altered the FDA's conclusion establishes that a disputed issue of material fact should have prevented entry of summary judgment on the defendants' preemption claim.

In re Incretin-Based Therapies, 721 Fed.Appx. at 584. Defendants' other arguments about preemption are irrelevant until they somehow overcome *both* of those issues, and yet their brief makes no mention of either.

1. Defendants' FDA Inaction Argument Was Presented To And Rejected By The Supreme Court in *Albrecht*.

Defendants argue that the FDAAA amendments of 2007, such as 21 U.S.C. § 355(o)(4), make FDA "inaction" represent "clear evidence." *See* DEF MEM, p. 4, 7, 9, 12, 18, 19, 35 (arguing FDA has a "labeling mandate under FDAAA," and so the lack of an FDA-mandated warning creates preemption). Defendants neglect to mention that they presented this argument to the Supreme Court and the Court rejected it. See *Albrecht Brief for Petitioner Merck*, pp. 5, 31-32, 38; *Reply for Petitioner Merck*, pp. 5, 7; *Brief for amici curiae of Pharmaceutical Research and Manufacturers of America,* pp. 3-18.

If the Supreme Court had accepted this argument, *Albrecht* would have ended with a judgment in Merck's favor, given that "FDA [had] long been aware that Fosamax could theoretically increase the risk of atypical femoral fractures." *Albrecht* at 1674-1675. Yet this argument was rejected. The Supreme Court instead placed new limitations on how a drug company can establish preemption, thereby preserving Congress's purposes in passing the FDCA without any preemption clause and ensuring state tort law was not displaced by judicial speculation. Under *Albrecht*, no amount of FDA "attention," "consideration," or "focus" can create preemption. Preemption occurs solely when the defendant drug manufacturer shows that it "fully informed the FDA of the justifications for the warning required by state law and that the FDA, in turn, informed the drug manufacturer that the FDA would not approve a change to the drug's label to include that warning" by way of an "agency action carrying the force of law." *Id.* at 1672, 1679.

Defendants recognize their argument is incompatible with *Albrecht*, so they urge this Court to rely on Justice Alito's *concurring* opinion—which carries no weight whatsoever—rather than the *majority* opinion binding on this Court. DEF MEM, p. 18. Notably, Justice Alito refused to join the majority opinion precisely because the majority rejected these same

arguments based on the FDAAA.[9] If the six Justices who joined the majority opinion had found merit in the argument that FDA inaction creates preemption, they would have joined Justice Alito's opinion. They did not.

2. Defendants' "Newly Acquired Information" Argument Contradicts *Albrecht*, Contradicts The Ninth Circuit's Opinion, And Improperly Flips The Burden To Plaintiffs.

It is already the law of this case that the Defendants failed to show the information they withheld from the FDA was immaterial, thereby precluding the entry of summary judgment on preemption. *In re Incretin-Based Therapies*, 721 Fed.Appx. at 584 (disputed issue of material fact should have prevented entry of summary judgment on preemption claim). *Albrecht* does not undermine that holding; it confirms that a drug manufacturer's failure to show it "fully informed" the FDA and provided "all material information," renders preemption unavailable. Accordingly, Defendants' motion must be denied.

a. Defendants' reliance on *Pradaxa Cases* is Misplaced.

Defendants recognize this issue, like the FDA agency action issue discussed above, bars any preemption defense, so again they attempt to override the Supreme Court, the Ninth Circuit, and this Court's prior factual findings by way of a short passage in an unpublished California trial court opinion:

> If the newly acquired information meets the definition outlined in 21 C.F.R. § 314.3(b), it also cannot be rooted in conjecture or hypothesis. Rather, it must conclusively establish, by scientifically valid measurable and statistically significant data, that the different or increased risks are actual and real. (See *Roberto*, supra, 2019 WL 4806271, *13 ("There is some case law… in the approved labeling.").

[9] Justice Alito did not join the majority opinion because, he complained, it "barely notes" the 2007 amendments. In his view, the majority should have held the amendments meant that, "if the FDA declines to require a label change despite having received and considered information regarding a new risk, the logical conclusion is that the FDA determined that a label change was unjustified." *Albrecht* at 1684 (Alito, J., concurring).

Pradaxa Cases, No. CJC-16-004863, 2019 WL 6043513, at *3 (Cal. Super. Ct. Nov. 08, 2019); cf DEM MEM, pp. 15, 25. *Roberto*, an unpublished Connecticut trial court opinion, does not make this argument, and neither *Pradaxa Cases* nor Defendants cite any basis for this astonishing misinterpretation of the law. Nor could they: there is no basis in *Levine*, *Albrecht*, the Ninth Circuit's opinion in this case, the FDCA, or the FDA's regulations for the claim that impossibility preemption requires Plaintiffs to "conclusively establish" an increased risk by "statistically significant data" that was "not previously submitted to the FDA." DEF MEM, p. 15. Such a rule would render *Albrecht* a nullity—the entire burden would be placed on the plaintiff, while the drug manufacturer would not be required to show anything at all. Such a rule would also set a far higher bar than the actual standards set by the FDA for when a drug manufacturer is required to update its labeling,[10] and far higher than the standard for *Daubert*.[11]

The claim made by *Pradaxa Cases* is plainly wrong and is not even viable in California state courts. Less than three weeks after Defendants submitted their brief in this case, the California Court of Appeal reiterated that the burden was *not* on the plaintiffs, that "impossibility preemption requires the drug manufacturer to show that it fully informed the

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[10] For warnings, 21 CFR 201.57(c)(6) provides, "the labeling must be revised to include a warning about a clinically significant hazard as soon as there is *reasonable evidence of a causal association* with a drug; *a causal relationship need not have been definitely established*." (Emphasis added.) For adverse events, 21 CFR 201.57(c)(6) provides they should be included if "there is *some basis to believe there is a causal relationship* between the drug and the occurrence of the adverse event." (Emphasis added.) Neither of these requires "conclusive" evidence or "statistically significant data." Moreover, as the Supreme Court held, "[a] lack of statistically significant data does not mean that medical experts have no reliable basis for inferring a causal link between a drug and adverse events," and "[t]he FDA similarly does not limit the evidence it considers for purposes of assessing causation and taking regulatory action to statistically significant data." *Matrixx Initiatives, Inc. v. Siracusano*, 563 U.S. 27, 40-41 (2011).

[11] See *Wendell v. GlaxoSmithKline LLC*, 858 F.3d 1227, 1235-1236 (9th Cir. 2017)(noting "statistically significant results" were not required to establish causation, and reversing district court for holding that experts must "rely on animal or epidemiological studies").

FDA," and that "hypothetical labeling changes and speculative future rejections are not clear evidence of an impossibility preemption defense." *Risperdal & Invega Cases*, 49 Cal.App. 942, 2020 WL 2896715, at *10 (Cal. Ct. App. May 8, 2020).

In *Risperdal & Invega Cases*, the drug manufacturer had formally proposed a warning label for the condition at issue along with the justifications for it (unlike Defendants here) and the FDA had issued a Complete Response Letter approving the warning (unlike Defendants here). The California Court of Appeal nonetheless reversed the trial court's grant of preemption because the drug manufacturer failed to provide the FDA with a table of calculations, even though that table "did not reveal risks of a different type or greater severity or frequency and the analysis was based on the studies submitted to the FDA," "the FDA confirmed that [the manufacturer] submitted all the necessary data and information to conclude that [the drug] was appropriately labeled," and there was a denied citizens petition in which "the allegations in the citizens petition were similar and partly based on some of the evidence presented here." *Id.* at *9-10.

Plaintiffs do not believe this Court should rely on unpublished California state court decisions when controlling precedent from the Supreme Court and the Ninth Circuit provide multiple reasons why Defendants' preemption defense must fail. Nonetheless, the fact that Defendants chose as their standard-bearer for preemption an unpublished state trial court decision that has already failed within the state's own appellate courts is indicative of the profound weakness of their position.

b. Defendants' other "newly acquired information" cases are similarly unhelpful.

Beyond *Pradaxa Cases*, Defendants have sprinkled their brief with references to a handful of federal cases, most of which were decided before *Albrecht* (like *Gibbons, In re Celexa*, *Dolin*, and *Utts*), or which have nothing to do with impossibility preemption in branded drug cases (like *Durnford*, *Knox*, *Murphy*, and *PLIVA*). For the post-*Albrecht* cases involving branded drugs (*Cerveny*, *McGrath*, and *Ridings*), Defendants make no effort to

explain these cases, instead preferring to quote a few cherry-picked words or to include them in a list of citations.

In *Cerveny*, for instance, the issue of preemption was decided prior to *Albrecht*, and the Court limited its discussion of *Albrecht* to a single footnote about why it was not disturbing its prior ruling. *Cerveny v. Aventis, Inc.*, 783 Fed.Appx. 804, 808 n. 9 (10th Cir. 2019). Yet even *Cerveny* derails Defendants' argument: the Court noted preemption was unavailable unless the drug manufacturer "supplied the FDA with an evaluation or analysis concerning the specific dangers," which none of the Defendants here have done. *Id.* Defendants also cite *McGrath v. Bayer Healthcare Pharm., Inc.*, 393 F.Supp.3d 161 (E.D.N.Y. 2019) as supportive of the *Pradaxa Cases*. See DEF MEM pp. 15, 25. But *McGrath* does not at any point compel a plaintiff to "conclusively establish" the increased risk by "statistically significant data."

Put simply, nothing in *Albrecht* states, implies, or even allows for any situation in which the Defendants can avoid their burden by claiming the *Plaintiffs* must make some initial showing. This same argument was made in the testosterone replacement therapy litigation and swiftly rejected:

> Actavis argues that Martin's claims are preempted because he has not identified "newly acquired information" discovered between April 2012, when the FDA approved a new Androderm label, and October 2012, when he was first prescribed Androderm. … Actavis's argument is unpersuasive because it assumes that the FDA's approval of the Androderm label in April 2012 constitutes 'clear evidence' that it would have rejected an attempt by Actavis to add the relevant warnings between 1995 and October 2012 based on the information available during that time.

In re Testosterone Replacement Therapy, 430 F.Supp.3d at 529-30.

There are multiple problems with Defendants' argument—*Albrecht* specifically rejected "hypothetical or potential conflict[s]," and obviously an imaginary FDA rejection of an imaginary CBE cannot possibly "carry the force of law"—but the most glaring is: Defendant Merck made exactly this same argument to the Supreme Court. In *Albrecht*, Merck began its Opening Brief, "Merck told the FDA what it knew about the link between

its drug Fosamax and the risk of atypical femoral fractures" and began its Reply Brief, "Respondents do not dispute that Merck shared the available scientific data with the FDA." Defendant Merck itself asked the Supreme Court to find preemption on the grounds that it had not withheld any newly acquired information and the Supreme Court refused.

B. *ALBRECHT* REQUIRES DEFENDANTS ESTABLISH THAT FDA INFORMED THE DRUG MANUFACTURER IT WOULD NOT APPROVE THE LABEL BY WAY OF AGENCY ACTION "CARRYING THE FORCE OF LAW." THE FDA HAS NEVER TAKEN ANY SUCH ACTION.

Albrecht made clear *why* preemption is a question for the judge, not the jury: because "[t]he underlying question for this type of impossibility pre-emption defense is whether **federal law** (including appropriate FDA actions) prohibited the drug manufacturer from adding any and all warnings to the drug label that would satisfy state law. " *Albrecht* at 1678 (emphasis added). Preemption is an issue of law for the judge to decide precisely because it involves interpreting the law and does *not* involve factual inferences or hypotheticals.

1. Defendants Cannot Point To A Single FDA Action Carrying The Force Of Law That Would Prohibit Them From Changing Their Labels Via The CBE Process.

Before *Albrecht*, the Ninth Circuit had already "declin[ed] to afford preemptive effect to agency actions that do not carry the force of law under *Mead* and its progeny." *Reid v. Johnson & Johnson*, 780 F.3d 952, 964 (9th Cir. 2015)(finding an FDA warning letter lacked preemptive effect because it was not the sort of agency pronouncement that Congress intended to carry the "force of law"). In *Albrecht*, the Supreme Court adopted the same approach for impossibility preemption in branded drug lawsuits:

> The Supremacy Clause grants "supreme" status only to the "the Laws of the United States." And pre-emption takes place only when and if the agency is acting within the scope of its congressionally delegated authority, for an agency literally has no power to act, let alone pre-empt the validly enacted legislation of a sovereign State, unless and until Congress confers power upon it. Federal law permits the FDA to communicate its disapproval of a warning by means of notice-and-comment rulemaking setting forth labeling standards, by formally rejecting a warning label that would have been adequate under state law, or with

> other agency action carrying the force of law. The question of disapproval "method" is not now before us. And we make only the obvious point that, whatever the means the FDA uses to exercise its authority, those means must lie within the scope of the authority Congress has lawfully delegated.

Id. at 1679 (citations and quotations omitted). In this case, the FDA has done nothing remotely resembling what the Supreme Court requires to establish preemption, and Defendants do not attempt to point to *any* agency action carrying "the force of law":

- **Supreme Court list of FDA actions that can establish preemption because they bear the force of law:**
  - Notice-and-comment rulemaking.
  - Formal rejection of warning label that would have complied with state law.
  - Other agency actions carrying the force of law:
    - See 21 U.S.C. § 355(o)(4)(A) (statute describing process for mandating a labeling change, including formal notification and dispute resolution).
- **Defendants' list of FDA actions they ask be deemed sufficient to establish preemption even though none of them bear the force of law:**
  - *Internal FDA Memoranda*: 2009 FDA internal memoranda obtained via FOIA requests. See DEF FACT No. 13.
  - *FDA Safety Communications*: March 2013 FDA Drug Safety Communication: FDA Investigating Reports of Possible Increased Risk of Pancreatitis and Pre-Cancerous Findings of the Pancreas from Incretin Mimetic Drugs for Type 2 Diabetes. See DEF FACT No. 14.
  - *Journal Articles*: February 2014 article published in NEJM (but not on FDA website, and not formally sent to Defendants) by employees from the Dutch Medicines Evaluation Board, the Swedish Läkemedelsverket, the European Medicines Agency, and four FDA employees, none of whom had the authority to approve or reject labeling changes to Defendants' drugs. See DEF FACT No. 15.
  - *Citizen Petitions*: March 2014 denied Citizen Petition requesting Victoza be withdrawn from the market, primarily for pancreatitis concerns, which did not present any of the nonclinical or clinical new safety information identified by Plaintiffs and which expressly disclaimed a request for any labeling change. See DEF FACT No. 21.
  - *FDA Briefing Books*: (1) September 2014 FDA Advisory Committee Briefing Book for Saxenda weight loss indication. See DEF FACT No. 22. (2) July 2017 FDA Advisory Committee Briefing Book for LEADER results. See DEF FACT No. 24. Both of these Briefing Books also contained disclaimers that they did not even necessarily reflect the final position of the reviewers who authored the sections.

- *Unrelated Label Changes*: "Nearly 100 labeling changes for the medications at issue in this MDL," none of which related to pancreatic cancer. See DEF FACT No. 27.

None of the FDA actions listed by the Defendants even "informed the drug manufacturer that the FDA would not approve a change to the drug's label to include that warning," *Albrecht* at 1672, much less did so "carrying the force of law." The NEJM article, for example, expressly does not represent the FDA's position, does not bind the agency, and does not carry the force of law against other parties. See 21 CFR 10.85(k)(providing that statements by FDA employees, even in writing, are "an informal communication that represents the best judgment of that employee at that time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed" unless the statement is a formal advisory opinion or part of a formal guidance, neither of which apply to the NEJM article).

The Third Circuit has held that not even a letter rejecting a PAS related to the risk at issue which warned about misbranding constituted "agency action taken pursuant to the FDA's congressionally delegated authority," because the misbranding reference is merely "stock language," rather than an agency action carrying the force of law. *In re Avandia Mktg.*, 945 F.3d 749, 760 (3d Cir. 2019). As the Eastern District of Pennsylvania put it:

> In making a preemption argument, it is not sufficient for the proponent to contend that if it had submitted a new label—with additional warnings—to the FDA, the FDA *would have* rejected the warning. In other words, the conflict must be real… Preemption is further limited in state law failure-to-warn situations where the FDA has *actually* rejected a proposed labeling change through action "taken pursuant to the FDA's congressionally delegated authority."

Crockett v. Luitpold Pharm., Inc., 2020 WL 433367 at *7 (E.D. Pa. Jan. 28, 2020)(some citations omitted); accord *Atkinson v. Luitpold Pharm., Inc.*, 2020 WL 1330705 at *3 (E.D. Pa. Mar. 23, 2020).

The Seventh Circuit has held the same. Defendants' brief strangely cites only the pre-*Albrecht* decision in *Dolin* (which Defendants remarkably suggest is consistent with the *Pradaxa Cases* dicta) without even mentioning the Seventh Circuit's post-*Albrecht* decision in the case. That very recent decision found that *Albrecht* appeared to have abolished impossibility preemption based on what the FDA "would have" done:

> The phrase "would not have approved" [in *Levine*] implies that the defendant may be able to satisfy the standard without showing that it actually requested a change for the label and that the FDA rejected it. In *Albrecht*, the Court wrote that the "clear evidence" needed is "evidence that shows the court that the drug manufacturer fully informed the FDA of the justifications for the warning required by state law and that the FDA, in turn, informed the drug manufacturer that the FDA would not approve a change to the drug's label to include that warning." 139 S. Ct. at 1672. That language implies that the manufacturer must have actually requested a change and that the FDA rejected it.
>
> In addition, further language in *Albrecht* can be read to signal that the FDA's rejection must have acted "pursuant to the FDA's congressionally delegated authority," citing as examples notice-and-comment rulemaking or a formal rejection pursuant to regulations or some other action "carrying the force of law." 139 S. Ct. at 1679. That language could be understood as indicating that less formal exchanges of correspondence, like some of the evidence in this case, are not enough to provide such "clear evidence."

Dolin v. GlaxoSmithKline LLC, 951 F.3d 882, 890 (7th Cir. 2020). The reason the preemption result in the 2018 *Dolin* decision referred to by Defendants stayed the same in 2020 is because "[a]s we read *Albrecht*, the 2007 formal requirement that all SSRIs carry the same warning label would qualify as 'agency action[] taken pursuant to the FDA's congressionally delegated authority.'" *Id.* at 891, quoting *Albrecht*. In this case, there has never been any "formal requirement" or any other agency action taken pursuant to the FDA's congressionally delegated authority that would preclude the Defendants from including a pancreatic cancer warning.

2. Defendants Cannot Establish FDA Informed Them It Would Not Approve Changing The Drugs' Label To Include A Warning.

As described above, Defendants' favored materials, like FDA internal memoranda and the NEJM article, are by law merely "informal communications," because 21 CFR 10.85(k) expressly precludes FDA employees from binding the agency at all except in very narrow circumstances, such as formal advisory opinions. These are all far short of the agency action carrying the force of law required by *Albrecht*. Moreover, none of the materials relied on by Defendants even do what *Albrecht* requires, which is "inform[ ] the drug manufacturer that the FDA would not approve changing the drug's label to include that warning." *Albrecht* at 1672.

For example, the 2014 NEJM article states, "[t]he FDA and the EMA have not reached a final conclusion at this time regarding such a causal relationship;" the 2014 citizen petition denial says the data is "indeterminate;" and the 2017 Advisory Committee Briefing Book for liraglutide states the clinical data "were inconclusive." Even if these materials were inexplicably granted the force of law, none of them informed the drug manufacturer that the FDA would not approve changing the drug's label. Defendants' *inference* that the statements *imply* that a CBE *would* be rejected is, first, the exact sort of "hypothetical" preemption argument *Albrecht* prohibits,[12] and second, is simply incorrect. "The FDA's statement that studies and trials have been 'inconclusive for determining risk' does not equate to a conclusion that reasonable evidence of a causal association is lacking." *In re Testosterone Replacement Therapy*, 430 F.Supp.3d at 530.[13]

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[12] See, e.g., *In re Avandia, Crockett*, and *Dolin*, *supra*.

[13] Notably, the "inconclusive" statement at issue in *In re Testosterone Replacement Therapy* came from the FDA-approved labeling itself, a source with a far better claim to "carrying the force of law" than a journal article or an advisory committee briefing book, and yet the court still denied preemption.

The Supreme Court has "cautioned many times before" that the "possibility of impossibility is not enough" and that "the existence of a hypothetical or potential conflict is insufficient to warrant the pre-emption of the state statute." *Albrecht* at 1678-1679. The court's task is simple once Defendants' multi-layered hypotheticals are set aside: "the judge must simply ask himself or herself whether the relevant federal and state laws irreconcilably conflict." *Albrecht* at 1679 (quotation omitted). Since there is no evidence of any FDA action bearing the force of law that says Defendants cannot add a pancreatic cancer warning, there is no conflict with state law, and hence no preemption.

C. *ALBRECHT* REQUIRES DEFENDANTS ESTABLISH THEY "FULLY INFORMED THE FDA OF THE JUSTIFICATIONS FOR THE WARNING." DEFENDANTS HAVE NOT AND CANNOT DO SO.

It is not necessary for this Court to even reach this prong of *Albrecht*. The Defendants cannot show that FDA "informed the drug manufacturer that the FDA would not approve a change to the drug's label to include that warning," much less that FDA did so by way of an agency action "carrying the force of law," and so preemption fails as a matter of law. *Albrecht* at 1672, 1679. But if the Court did reach this issue, it would find more reasons why Defendants' motion must be denied.

1. For A Drug Manufacturer To Show It "Fully Informed The FDA Of The Justifications For The Warning," It Must Show It Submitted A Comprehensive Evaluation Or Analysis Supporting The Warning. A Drug Manufacturer Cannot Merely Point To Scattered Information Available To The FDA.

As described in Section II(B), Defendants' argument is based upon erroneous claims that the FDA is presumed to be fully informed, and that the *Plaintiffs* have a burden to show the FDA was *not* fully informed. This is the opposite of what the Supreme Court held in *Albrecht*, which requires the drug manufacturer to show "that it fully informed the FDA of the justifications for the warning required by state law." *Albrecht* at 1678. It is telling – and not surprising – that Defendants' brief never even mentions the words "fully informed" or "justifications." Defendants know they cannot meet either requirement.

The instant case is similar in this respect to the *In re Testosterone Replacement Therapy* cases pending in the Northern District of Illinois:

> Actavis does not offer evidence that it fully informed the FDA of the justifications for the warnings that Martin contends were necessary. It does not even offer evidence that it *partially* informed the FDA of those justifications. Likewise, Actavis does not offer evidence that the FDA informed it that the FDA would not approve a change to Androderm's label to include the warnings at issue, let alone that the FDA did so through an action it took pursuant to congressionally delegated authority. Actavis cannot satisfy the clear evidence standard without this sort of proof.

Id., 430 F.Supp.3d at 531 (citations and quotations omitted; emphasis in original).

Like the defendants in *In re Testosterone Replacement Therapy*, the Defendants in this case have not even *partially* informed the FDA of the justifications for a pancreatic cancer warning. They are thus missing the essential "fully informed" element of their preemption defense.

2. The Law Of The Case Holds That Defendants Failed To Provide The FDA With Material Safety Information.

Even if Defendants' legal arguments were erroneously adopted *in their entirety*, preemption is still unavailable as a matter of law. As the Supreme Court recognized, when assessing whether a drug manufacturer has "fully informed" the FDA, the parties might dispute "whether the drug manufacturer submitted all material information to the FDA," and it would be for the court to decide that factual issue. *Albrecht* at 1680. This Court and the Ninth Circuit have already examined the record relating to Health Canada, the clinical trial imbalances for sitagliptin and liraglutide, the primate studies in exenatide, and the secondary analysis of liraglutide in rodents, and found that Defendants failed to submit all material information to the FDA:

> [I]n its discussion of the materiality of the "new safety information," the district court stated, "it *remains unclear whether the FDA considered this information, and if it did not, whether this data would have altered the FDA's conclusion.*" Uncertainty about whether the FDA considered the "new safety information" and whether it would have altered the FDA's conclusion establishes that a disputed issue of material fact should have prevented entry of summary judgment on the

> defendants' preemption claim. As the district court correctly noted, the parties' experts disputed whether the "new safety information" would have been material to the FDA's analysis.

In re Incretin-Based Therapies, 721 Fed.Appx. at 584 (emphasis in original). It is the law of the case that the Defendants failed to submit all material information to the FDA, and thus Defendants are not entitled to summary judgment.[14]

Defendants make no effort to address this issue, except to erroneously assert, without explanation, "The Ninth Circuit directed this Court to consider the materiality of that information." DEF MEM, p. 20. The Ninth Circuit did no such thing. It recognized that this Court "correctly" found a genuine dispute between the parties' experts on the materiality of the information; recognized this Court had found "uncertainty" about what the FDA would have done with that information; and then explicitly held that such uncertainty meant Defendants had failed to establish the information was immaterial.

Defendants repeatedly reference Plaintiffs' decision not to update Dr. Fleming's report as if it reflects some sort of concession. DEF MEM, pp. 2, 9, 14, 19, 20, 21, 35. That is hardly the case: the Plaintiffs bear no burden on preemption; Defendants plainly cannot meet any of the elements required by *Albrecht*; the Ninth Circuit *already* held that Defendants failed to provide the FDA with material new safety information; and any ancillary factual issues are to be decided by the Court. To the extent there is any unusual gap in expert testimony here, it is on the part of Defendants and their decision not to supplement Dr. Goldkind's report following the *Albrecht* decision. *Albrecht* "requires the drug manufacturer to show that it fully informed the FDA of the justifications for the warning," *Albrecht* at 1678, and notes "the litigants may dispute whether the drug manufacturer submitted all material information to the FDA." *Id.* at 1680. Yet Defendants'

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[14] "The law of the case doctrine states that the decision of an appellate court on a legal issue must be followed in all subsequent proceedings in the same case." *In re Rainbow Magazine, Inc.*, 77 F.3d 278, 281 (9th Cir. 1996)(quotation omitted).

only preemption expert reviewed literally nothing that would help answer either question[15] and testified that his entire opinion depended on his assumption that it was irrelevant whether the Defendants had informed the FDA of anything at all:

> Q. Now, sir, because like you said, changes being effect[ed] relates to new safety information that a sponsor has, don't you think it's important when someone like you is going to give an opinion on whether the FDA would accept or reject a CBE, that you know if the sponsor has any new safety information pertaining to that CBE?
> A. Based on the exhaustive review that the FDA did, I don't believe that -- I can't conceive of any information that would, that would add insight in – to the FDA's decision.

Goldkind Dep., 80:15:81-1, Ex. 6. Dr. Goldkind's inability to "conceive of any information" that would be material to the FDA regarding pancreatic cancer doubtless explains why his report was not supplemented, but even if it had been, the Ninth Circuit's findings on materiality and the Supreme Court's decision in *Albrecht* had already closed the door to preemption.

3. Defendants Failed To Provide The FDA With Material Safety Information.

Again, it is unnecessary for the Court to even reach this issue. It would also be reversible error for the Court to revisit this issue and reach a new conclusion that differed from the Ninth Circuit, but for completeness, Plaintiffs note that Defendants' argument fails at this level, too.

a. The previously identified information is material and shows defendants did not fully inform the FDA of the justifications for a warning.

Defendant Merck admits it never submitted to FDA the signal assessment by Health Canada and it still does not know if the FDA ever reviewed the signal assessment, much less if the FDA reviewed it prior to the 2014 NEJM article.[16] Defendant Merck also admits

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[15] See Goldkind Materials Review, Ex. 5.

[16] See DEF MEM, p. 23 ("whether the FDA has reviewed it or not").

that it submitted inaccurate information about pancreatic cancer in its clinical trials to the FDA,[17] omitting half of the pancreatic cancers in sitagliptin, thereby creating the false impression of an equal number of cases in sitagliptin and comparators. Defendant Merck also admits that the 2014 NEJM article includes a citation to a Merck-sponsored article[18] that was wrong at the time it was published and that, to this day, Merck has never informed the FDA of the issue.[19] This evidence is so compelling that even Defendants' own regulatory expert, Dr. Goldkind, admitted at deposition that an imbalance in clinical trials could have affected FDA's assessment. Goldkind Dep., 154:10-160:14, Ex. 6.

Defendant Amylin does not dispute that it falsely claimed to the FDA and the medical community that "no dysplastic lesions, pancreatic intraepithelial neoplasia (PanIN), or lesions resembling pancreatic cancer were observed in any pancreatic specimen examined at baseline or after treatment in either animal group"[20] in a 14-week study of baboons. [redacted] [21] Defendants' own motion acknowledges that this information

[17] See, e.g., [redacted]

[18] Footnote 3 of the NEJM article cites Engel SS, et al, Safety and tolerability of sitagliptin in type 2 diabetes: pooled analysis of 25 clinical studies. Diabetes Ther 2013;4:119-145, which, like Merck's submission to the FDA, excluded 3 trials containing sitagliptin pancreatic cancer cases while not excluding any trial with comparator cases.

[19] Merck's argument is, incredibly, that the TECOS results they provided years later and which the FDA rejected would somehow retroactively absolve them of the misleading 3-to-3 clinical trial imbalance they provided to the FDA. See DEF MEM, pp. 23-28.

[20] Fiorentino TV, et al, "Chronic Continuous Exenatide Infusion Does Not Cause Pancreatic Inflammation and Ductal Hyperplasia in Non-Human Primates," Am J Pathol. 2015 Jan;185(1):139-50. Ex. 7.

[21] [redacted]

would be material to the FDA, given the Defendants' reliance on the NEJM article's statement that studies did *not* find "overt pancreatic toxic effects," and Defendants' own argument that "pre-cancerous lesions" in animals would be material to the FDA. DEF MEM, pp. 11, 22, 33. [redacted]

Defendant Novo admits that it reported to the FDA and the medical community "no effect on the exocrine pancreas" in a 13-week ZDF rat study, DEF MEM, p. 31, even as it chose not to report to the FDA or the medical community an internal secondary analysis of that same study which found [redacted] Further discovery has revealed that Lotte Knudsen, the "Scientific VP" for incretins and "Scientific Coordinator" for preclinical studies, [redacted]

4. Discovery Has Revealed More Material Safety Information That Defendants Failed To Provide To The FDA.

a. [redacted]

In January 2010, the FDA imposed on Novo several post-marketing requirements, including a requirement Novo study "the effects of liraglutide on the exocrine pancreas in a rodent model of insulin-resistant type 2 diabetes mellitus," including "a thorough assessment of macroscopic and microscopic pathology of the pancreas including pancreatic

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[redacted]

[22] Dkt 1166-21: Vrang, et al., The Effects of 13 Wk of Liraglutide Treatment on Endocrine and Exocrine Pancreas in Male and Female ZDF Rats: A Quantitative and Qualitative Analysis Revealing No Evidence of Drug-induced Pancreatitis. Am.J.Physiol.Endocrinol. 2012 Jul 15; 303(2): 253-264. [redacted]

exocrine cell and ductal cell proliferation/metaplasia."[23] The FDA did not know, and Novo never told the FDA, that Novo [redacted]

The concealment of that data was not an isolated incident. As described above, subsequent discovery revealed that Novo not only failed to tell the FDA about its secondary analysis of ZDF rats in yet another study. [redacted]

[23] Ltr. from U.S. Food and Drug Administration to Novo Nordisk Approving NDA 022341 (January 25, 2010), p. 1, available online at: http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/022341s000ltr.pdf

[24] [redacted]

[redacted] several months before the NEJM article said the FDA was unaware of any "overt pancreatic toxic effects" in animal studies. Instead of informing the FDA of this finding, Novo concealed it, [redacted]

[redacted]

[redacted]

b. Novo performed a study of over 200,000 diabetics matched to the LEADER population to find the expected rate of pancreatic cancer in LEADER; never disclosed it; and then lied to the FDA about that expected rate.

Defendants rely heavily on materials relating to the FDA's LEADER Advisory Committee in 2017. DEF MEM, pp. 10-11, 20, 34. Novo did not merely fail to "fully inform" the FDA and the Advisory Committee about LEADER; Novo outright lied to them.

Novo's briefing document for the LEADER Advisory Committee notes that EAC-confirmed malignant pancreatic neoplasms occurred in the liraglutide arm at a rate of 0.08 per 100 patient-years and in the placebo arm at a rate of 0.03 per 100 patient-years.[25] NNI-MDL 01367497 (Ex. 19, p. 79). Novo claims the higher rate in the liraglutide arm is of no concern because it aligns with the expected rate of pancreatic cancer, whereas the placebo rate is unusually low:

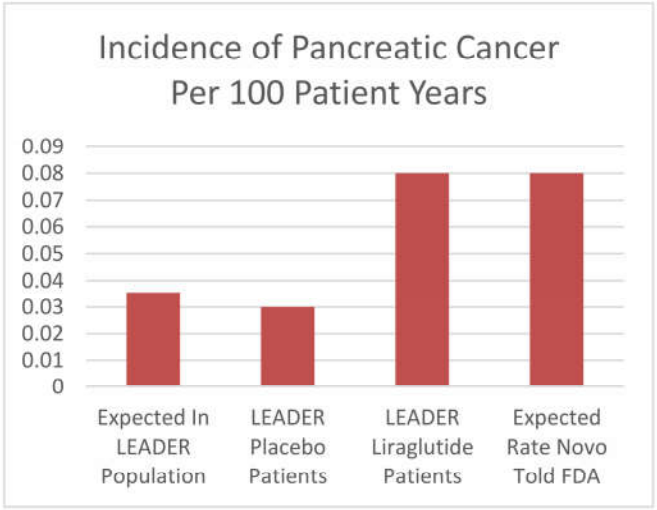
> In summary, though the incidence of EAC-confirmed malignant pancreatic neoplasms in LEADER was low, more events occurred in the liraglutide group compared with the placebo group. The reported event rate for the liraglutide group (0.08 events per 100 PYO) is within the predicted range as may be expected for the background T2DM population (ranging from 0.05-0.08 events per 100 PY) and did not increase over time.

Id., p. 81. That is false. Novo knew the "the predicted range" of "background" pancreatic malignancies in LEADER was not a generalized guess of "0.05-0.08" for all type 2 diabetics, but a robustly calculated 0.03565 (95% CI: 0.02423-0.0559) for the exact population in LEADER. Novo knew the LEADER placebo rate aligned with the background rate, whereas the LEADER liraglutide rate was elevated well beyond statistical significance, as discussed below.

[25] The term used by Novo's brief is "patient years of observation," or "PYO."

While LEADER was ongoing, Novo hired Optum[26] to conduct a massive electronic records study using the Humedica database, scouring the records of millions of patients to identify 431,355 patients who met the same eligibility criteria as LEADER, then analyzing those patients' records in depth to find the expected rate for pancreatic malignancies in a population matched precisely to the same population enrolled in LEADER, including matching by age, gender, race, ethnicity, weight, body mass index, hypertension, hyperlipidemia, smoking status, coronary artery disease, chronic pancreatitis, specific prior antidiabetic drug use, and myriad other demographic, clinical, and comorbidity covariates.[27] The "primary" cohort in the Humedica study involved an astonishing 208,672 patients, more than twenty times the size of LEADER, with the patients all matched and weighted to align with the 9,340 patients in LEADER. As one example of its enormous scope, for every single one of the 1,130 current smokers in LEADER, the Humedica study had more than 23 current smokers who also met the enrollment criteria of LEADER, while balancing the proportion of them in the cohort (12.8%) to align with LEADER itself (12.1%).

The Humedica study produced a "standardized incident rate" for "pancreatic malignancy" in the "LEADER-like cohort" of 35.65 per 100,000 patient-years (95% CI: 24.23-50.59), or 0.03565 per 100 patient-years—a figure strikingly similar to the *placebo* results of LEADER, in which the placebo group had an EAC-confirmed



[26] "We'll do the data dirty work," says their website: https://www.optum.com/solutions/data-analytics.html

[27] NNI-MDL_02111320 (May 2015 Final Report, Ex. 20). See, e.g., pp. 14-17 (listing dozens of covariates) and pp. 33 (Table 1b, showing the specific alignment between the study and LEADER on more than twenty covariates).

malignant pancreatic cancer rate of 0.03. The liraglutide group in LEADER, however, had an EAC-confirmed malignant pancreatic cancer rate of 0.08, more than *double* the 0.03565 rate found by the Humedica study's analysis of 208,672 patients specifically matched to the LEADER population.

The Humedica study would be of immense importance to the FDA—it shows the placebo rate in LEADER aligned with the background rate in the real-world, while the liraglutide rate was elevated far beyond the level of statistical significance—so Novo buried it. Novo never provided the FDA with the study, never published the results, and certainly never used it as part of "fully inform[ing] the FDA of the justifications" for a labeling change. Instead, Novo made up numbers to make the liraglutide arm in LEADER look normal.[28]

Novo has repeatedly lied to the FDA about the expected rate of pancreatic cancer in the LEADER trial ever since it ended. The most recent liraglutide Periodic Safety Update Report ("PSUR") provided in discovery, dated February 27, 2018, includes a specific section on pancreatic cancer.[29] The PSUR downplays LEADER as a statistical anomaly, claiming "most events presented shortly after randomization," and including a "background incidence" section that claims "incidence of pancreatic cancer in people with T2DM has been reported to be in the range of 0.1-2.4 per 1,000 person-years," *id.*, which is simply not true for LEADER. Novo performed a detailed study of 208,672 patients matched to the LEADER population specifically to find the background rate—0.03565 (95% CI: 0.02423-0.0559)—but, to conceal how damning the LEADER results were, they claimed to the FDA that the background rate could be nearly seven times higher than that.

[28] [redacted]

[29] NNI-MDL_00476876 (Ex. 22), PSUR section 16.4.2.4.

That is not the only glaring omission in the 5 pages devoted to pancreatic cancer in Novo's PSUR. Apart from LEADER, the PSUR includes two sections which aggregate pancreatic cancer cases from multiple trials. The first section, "Liraglutide in T2DM – Glycemic control trials," lists 3 cases in liraglutide and 0 in placebo, and the second section, "Liraglutide for WM [weight management]," lists 1 case in liraglutide and 0 in placebo. *Id.* Yet Novo's own internal "Surveillance Report" for October 2017 lists *four* cases in the glycemic control trials (NN2211) and *two* cases in the weight management program (NN8022).[30] This is not a mere typographical error: in the NN8022-1839 weight management program, the 1-year clinical trial report lists an "event of confirmed pancreatic cancer" involving patient [redacted],[31] while the 3-year clinical trial report lists an entirely different "EAC-confirmed pancreatic neoplasm" involving patient [redacted][32] For the glycemic control trials count, it is unclear which case was included on Novo's internal surveillance report yet secretly omitted from their PSUR, patient 627014 from trial NN2211-1436 or patient [redacted] from trial NN2211-3917? Neither was included in the PSUR, even though both should have been.

Novo has long known that liraglutide's clinical trials showed an association with pancreatic cancer. [redacted]

Novo's solution was to do the exact opposite of "fully informing the FDA of the justifications," instead chopping up their own data as much as possible, making it nearly

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[30] NNI-MDL_02592351 (Ex. 24).
[31] NNI-MDL_01279850 (Ex. 25), p. 414.
[32] NNI-MDL_02018586 (Ex. 26), p. 425.

impossible to create a coherent count of its pancreatic cancer cases, and repeatedly lying to the FDA about the cases in clinical trials and the expected incidence of cases in clinical trials. Novo has earned federal prosecution, not federal preemption.

c. Merck maintains secret nonclinical research projects with chemical analogs because [redacted]

[redacted]

[redacted]

Although Merck itself treated desfluorositagliptin as an "analog" of sitagliptin that could be used as a substitute for any type of nonclinical test, when the FDA sought information about a potential mechanism for pancreatic toxicity in 2009 [redacted]

(Ex. 34). The study[33] used C57BL/6 mice fed a high-fat diet, a common method for analyzing the effects of antidiabetic treatments. Dr. Drucker's lab excised pancreatic samples for histological analysis. This was a study that undoubtedly could have provided material safety information, but Merck did not obtain or review the samples to respond to the FDA, nor suggest FDA review them, solely because Dr. Drucker had used sitagliptin's analog, desfluorositagliptin (at Merck's suggestion). The study also was not listed in the nonclinical study charts Merck provided Plaintiffs in this litigation.

In November 2009, an FDA supervisor prepared a memorandum in response to Merck's submission.[34] The FDA supervisor determined that Merck's submission of preclinical studies was inadequate: "I disagree that the contribution of hyperglycemia to potential sitagliptin-induced pancreatic toxicity has been adequately evaluated." The FDA supervisor further noted that it would be helpful to have a rodent study involving a high-fat diet "because a HFD, and particularly high triglycerides, could impact the incidence of pancreatitis." The FDA supervisor also noted that studies conducted by academic investigators "could be relevant" if the study included "a thorough histological assessment of the pancreas that includes immunostaining with cell proliferation markers, and that the evaluation includes exocrine, endocrine, and ductal areas of the pancreas." Finally, the FDA supervisor concluded "none of the arguments [by Merck] are sufficient to address the gap in experimental data with sitagliptin in diabetic animal models." The FDA thereafter imposed a post-marketing requirement on Merck, including studies that performed a histological evaluation of the exocrine and endocrine pancreas, including ducts, and assessed cell proliferation markers.

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[33] Published as Lamont, BJ, and Drucker, DJ, "Differential Antidiabetic Efficacy of Incretin Agonists Versus DPP-4 Inhibition in High Fat–Fed Mice," Diabetes 2008 Jan; 57(1): 190-198.

[34] Ex. 35. Available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021995Orig1s013.pdf , p. 87.

Merck had multiple desfluorositagliptin studies that it could have used to provide the FDA with more of the exact kind of data the FDA sought, such as the Drucker study discussed above, which used a high-fat diet and which had preserved sections of the pancreas for histological assessment. Merck chose not to, instead preferring—as it had planned for years—to provide only the sitagliptin studies, which themselves were only ever performed because Merck knew in advance that the outcome would be favorable because it had first researched the issue with desfluorositagliptin.

Despite this Court's orders requiring disclosure of desfluorositagliptin, it is not possible for Plaintiffs to reconstruct more than a glimpse of Merck's desfluorositagliptin program. [redacted]

Again, the preemption burden is on *Merck,* not Plaintiffs. Merck's operation of an entirely separate nonclinical program for sitagliptin's analog, desfluorositagliptin, done for the purpose of concealing from the FDA information that Merck obtained about sitagliptin by testing desfluorositagliptin, is the opposite of "fully informing" anyone. Having learned how to hide its desfluorositagliptin data from the FDA, Merck proceeded to hide it from Plaintiffs as well, despite being under a court order to produce it.

Merck came to recognize desfluorositagliptin [redacted]

[redacted] The redacted name, and Merck's withholding of documents about this additional compound used for "for post-marketing support of Januvia," are not Plaintiffs' problem. *Merck* has the burden of showing it "fully informed the FDA of the justifications" for the warning, including "all material information." It was *Merck's* decision to create these secret compounds. and *Merck's* decision to keep them hidden from the FDA, the Plaintiffs, and this Court. Merck chose the path of deception and thus chose to fail this element of the *Albrecht* test.

d. Merck continues to misrepresent its pooled clinical trial data to FDA; has misrepresented the TECOS data; and has not informed the FDA of glaring problems specific to the TECOS pancreatic cancer results.

As shown above, Merck continues to misrepresent its clinical trial data to the FDA. Merck's Development Safety Update Report ("DSUR") for August 3, 2017, [redacted]

article. As discussed above, that calculation deliberately omitted from the "pooled" studies three clinical trials with pancreatic cancer cases in the sitagliptin arms, leading to the false assertion that there were 3 sitagliptin cases rather than 6, versus only 3 non-exposed cases. Merck's statement to the FDA about the "incidence of pancreatic cancer adverse experiences in pooled Phase I-III clinical studies" is false. If Merck "fully informed" the FDA, it would show the rate for sitagliptin users was double that for non-users.

Merck's DSUR also claims that in TECOS, [redacted]

Nonetheless, Merck still has not "fully informed" the FDA about other problems in TECOS. [redacted]

Randomization for TECOS began in December 2008 and the last patient visit was March 30, 2015. [redacted]

[35] [redacted]

[redacted] It is unknown, and now unknowable, how many pancreatic cancer cases TECOS lost as a result of this erroneous protocol for the first five years and two months of the trial.

Moreover, TECOS did not follow the original protocol or the amended protocol consistently: [redacted]

For most of the trial, the only way to be assured that a pancreatic cancer would be reported per protocol would be if it led to treatment discontinuation (Protocol 4.6.3). Those numbers are considerably worse for Merck, [redacted]

MRKJAN0003441527 (Ex. 44, p. 165).

Albrecht is explicit, requiring drug manufacturers to "fully inform the FDA of the justifications" for the warning. That would require Merck be forthright with the FDA about TECOS, but there is no indication Merck ever flagged any of these issues for the FDA. Instead, Merck affirmatively promoted the 9-to-14 numbers that it knew were irrevocably compromised by the flaws in the TECOS protocols.

e. Amylin misled the FDA and the medical community about its clinical trial data, which has consistently shown an elevated risk of pancreatic cancer, including in EXSCEL.

[redacted]

Internal Amylin Analysis, Ex. 45	Amylin's FDA Submission, Ex 46

[36] See AMYLN07333537, Ex. 45. (March 31, 2014 Presentation)
[37] See AMYLN07349049, Ex 46.

A few months later, in November 2014, researchers at Amylin submitted a journal article (which was later published and then submitted by Amylin to the FDA) in which they manipulated their selection of clinical trials to create the appearance of zero pancreatic cancers. In that article, Amylin trimmed the 35 trials from their original analysis down to 8 trials, then claimed "[t]here were no cases of pancreatic cancer reported in any group analyzed, although one case of pancreatic neoplasm was reported for exenatide BID."[38] Amylin had cherry-picked these studies to avoid the pancreatic cancers, but they failed at

[38] MacConnell, et al, "Safety and tolerability of exenatide once weekly in patients with type 2 diabetes: an integrated analysis of 4,328 patients," Diabetes Metab Syndr Obes. 2015; 8: 241–253. Ex 47. At the time of this study, Bristol-Myers Squibb owned Amylin, so the researchers are identified as from Bristol-Myers Squibb.

that, too: [redacted]

AMYLN06278411, Ex. 48, p. 103.

Amylin's justification for omitting this case was a decision not just to cherry-pick trials, but to cherry-pick the data within them, and look solely at the "24-week and 30-week comparator-controlled periods." That was, of course, contrary to their FDA submission, which suppressed the rate of pancreatic cancer by silently including clinical trials with no comparators *at all*. Amylin further misrepresented the nature of the trials, claiming they were not "long enough to observe rare AEs with a long course of development (eg, cancers)," when in fact the DURATION -1 trial had "long-term efficacy and safety of Exenatide LAR 2 mg once weekly (QW) evaluated over 364 weeks of therapy" and indeed had a pancreatic cancer, as described above. Ex. 48.

EXSCEL is no better. Initially, Amylin's EXSCEL results are, like Merck's TECOS results, the product of compromised data collection. The first patient was enrolled on June 18, 2010, [redacted]

[39] 2993LAR-105 (DURATION - 1), ClinicalTrials.gov Identifier: NCT00308139
[40] AMYLN08145357, Amendment 02, 10 May 2011, p. 12. Ex. 49.
[41] AMYLN07832169, Amendment 05, 25 October 2013, p. 17. Ex. 50.

[redacted] EXSCEL's management did not take pancreatic cancer seriously and so the investigators did not either.

An entirely separate problem with EXSCEL is that multiple positively-adjudicated pancreatic cancer cases in the placebo arm were documented using incretin mimetics after starting the trial and prior to their diagnosis, including:

- [redacted]

[42] AMYLN07208641 (Clinical Study Report Section 11.4.4.7), p. 8539. Ex. 51.
[43] AMYLN07208641, p. 481. Ex. 52.
[44] AMYLN06748007, pp. 31-32. Ex. 53.
[45] AMYLN07208641, p. 3494. Ex. 54.
[46] AMYLN07208641, p. 5839. Ex. 55.

[redacted]

The best number for EXSCEL, after cases are properly removed for protocol violations—such as multiple positively-adjudicated placebo cases diagnosed outside of the time limits required by the study protocol[49]—cannot be found in the FDA submissions or even in the body of the clinical study report, but instead requires digging into page 1703 of an appendix, which reveals the actual number of adjudicated pancreatic cancers per protocol: [redacted]
Yet even that number is still unduly favorable to exenatide for present purposes, [redacted]

[redacted]

It is Amylin's burden to prove it "fully informed the FDA of the justifications" for a pancreatic cancer warning. Amylin's persistent misrepresentation of clinical trial data and its failure to present FDA with an accurate, candid, and thorough evaluation of its clinical trials precludes the company from establishing this element of *Albrecht*.

V. CONCLUSION

For the reasons set forth above, Plaintiffs respectfully request that Defendants' Motion for Summary Judgment be denied.

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[47] AMYLN07208641, p. 6096. Ex. 56.
[48] AMYLN07208641, p. 6107. Ex. 57.
[49] [redacted]
[50] AMYLN06642214, p. 1703. Ex. 59.

Dated: July 8, 2020

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